

## Monkeypox Disease: History, Epidemiology, Threat Assessment, and Management Strategies

Nikhil Nath<sup>1</sup> , Kuldeep Dhama<sup>2</sup>  and Talha Bin Emran<sup>3,4\*</sup> 

<sup>1</sup>Department of Pharmacy, International Islamic University Chittagong, Chittagong 4318, Bangladesh.

<sup>2</sup>Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India.

<sup>3</sup>Department of Pharmacy, BGC Trust University Bangladesh, Chittagong, 4381, Bangladesh.

<sup>4</sup>Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh.

### Abstract

Infection with the monkeypox virus is more prevalent among genus *Funisciurus* squirrels, less prevalent among genus *Heliosurus* squirrels, and rare among forest monkeys. These squirrels inhabit secondary woods close to human settlements in rural Zaire, particularly where oil palm is cultivated. In Prime Rain Forest, they are in short supply. The monkeypox virus often affects children between the ages of 5 and 9, particularly in rural settings where children hunt and consume squirrels and other small animals. Animal husbandry will minimize the danger and occurrence of human monkeypox, even in areas where the virus has spread to squirrels, as the human population grows and relies primarily on animals for animal protein. Population expansion and economic development in West and Central Africa may lessen the danger of monkeypox infection in people, but visitors who interact with animals should be vaccinated against smallpox. The spread of monkeypox can be stopped by measures such as post-exposure vaccination, contact tracing, case identification, and isolation of infectious patients. The recent monkeypox incidence is of further concern in light of the current COVID-19 pandemic.

**Keywords:** Monkeypox, History, Epidemiology, Threat Assessment, Management Strategies

\*Correspondence: talhabmb@bgctub.ac.bd

**Citation:** Nath N, Dhama K, Emran TB. Monkeypox Disease: History, Epidemiology, Threat Assessment, and Management Strategies. *J Pure Appl Microbiol.* 2022;16(suppl 1):3062-3071. doi: 10.22207/JPAM.16.SPL1.02

© The Author(s) 2022. **Open Access.** This article is distributed under the terms of the [Creative Commons Attribution 4.0 International License](https://creativecommons.org/licenses/by/4.0/) which permits unrestricted use, sharing, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

## INTRODUCTION

Monkeypox is a zoonotic orthopoxvirus that develops sickness in people comparable to smallpox but with a far lower fatality rate. Because it is indigenous to western and central Africa, and outbreaks in the Western Hemisphere have been linked to the exotic pet trade and international tourism, this virus is medically essential. The orthopoxvirus genus, which belongs to the Poxviridae family, also includes the camelpox virus, cowpox virus, vaccinia virus, and variola virus, in addition to the monkeypox virus. The World Health Organization identified the virus in the 1980s. At that time, it was already widely believed to be the most widespread orthopoxvirus in the human population since the elimination of smallpox. Since its eradication, the virus has been confirmed to be at the top of the list of infectious diseases caused by viruses with the potential to be endemic or pandemic; this includes orthopoxvirus, Crimean-Congo hemorrhagic fever, Ebola virus disease, Hendra virus infection, influenza, Lassa fever, Marburg virus disease, MERS-CoV, SARS-CoV, Nipah virus infection, smallpox, yellow fever, Zika virus disease. These infections are on the rise all over the globe. They often manifest themselves with neurological symptoms. The monkeypox virus has reemerged as a serious international health risk because it poses new dangers and may spread easily across national boundaries. Due to these effects, the World Health Organization has issued a global health emergency declaration about hMPXV,<sup>1</sup> confirming the smallpox virus continues to harm the human population—loss of human population since smallpox eradication. The virus has been plaguing the human population since the eradication of smallpox.<sup>2,3</sup> The COVID-19 pandemic proved that infections with the ability to spread globally might cause damage to the neurological system.<sup>4</sup> Neurological conditions range from those affecting the central nervous system (such as meningitis, encephalitis, intraparenchymal hemorrhage, and seizures) to those affecting the peripheral nervous system (such as sensorimotor neuropathy, sensorineural hearing loss, and ophthalmoplegia), and even from post-infectious conditions to congenital ones (fetal microcephaly). Although the neurological manifestations of

certain illnesses, such as monkeypox virus (MPXV) infection, are not fully understood, there have been isolated instances of such manifestations.<sup>5</sup> The virus in question was responsible for the loss of the human population, as stated by the confirmation. The local monkeypox habitat has limited resources as a solid initiative for clinical identification, diagnosis, and prevention of monkeypox. These regions include places like Africa and South America. These regions consist of the following: Studies conducted after determining what has been successfully eradicated have found the monkeypox epidemic.<sup>6-8</sup> Smallpox and monkeypox are clinically quite similar. Symptoms of both illnesses, a high temperature and the development of a rash, manifest simultaneously after an incubation period of around ten days. Most instances of smallpox were classified as conventional smallpox, in which the exanthem developed in a centrifugal pattern over many days (e.g., macules, papules, vesicles, pustules, scabs). Thirty percent of those who became sick from it ultimately passed away. The development of increasing skin lesions defined neither the early nor the late hemorrhagic forms of the illness, and the former was virtually always fatal. Although, during an epidemic in the United States in 2003, physicians saw blood inside a patient's skin lesions, it is not widely believed that monkeypox causes hemorrhaging in humans. The fatality rate associated with monkeypox is substantially lower than that associated with smallpox (> 10%). Still, the symptoms are otherwise identical to those of either the classic or modified forms of smallpox. Lymphadenopathy, often associated with monkeypox but not smallpox has not been reported by physicians treating smallpox patients in the past.<sup>9</sup> Nevertheless, routine vaccinations against smallpox have been discontinued, requiring further study as the animal's immunity is relatively low. Also, basic environmental research is needed to understand better the species of animals involved in the virus's transmission and maintenance and how can administer preventive strategies. This study is necessary for two reasons. First, to better understand the animal species involved in the information and care of the virus. This is essential for two different reasons. Initially, research is needed to understand better the

species that play a role in the virus's spread and maintenance. Both have to prove that they are capable of fulfilling this responsibility.<sup>10-12</sup>

### Epidemiology of Monkeypox

Since the first cases were recorded in the 1970s, human monkeypox incidence has increased worldwide, with the Democratic Republic of Congo experiencing the most significant increase. From 2001 to 2016, monkeypox incidence varied from 0.64 per 100,000 to 50 cases per 10,000. South Sudan, Central African Republic, Democratic Republic of Congo, Nigeria, Ivory Coast, Liberia, Cameroon, Sierra Leone, and Gabon are included in this list. Congo is also included. The Democratic Republic of Congo presents an exceptionally difficult problem. Many West African countries have documented cases of monkeypox in humans.

On the other hand, since 1981, the region of central Africa known as the Congo Basin has reported the highest number of illnesses. The Democratic Republic of Congo (DRC) continues to record the highest number of human monkeypox cases annually.<sup>13</sup> It wasn't until May 13, several days after the first index case report — that it determined that two laboratory-confirmed and one suspected case were living in the same household. On May 15, a sexual health service in the UK confirmed four more cases of a vesicular rash in men who had sex with other men. At first, I thought the virus was only spreading locally in the UK, but the true source of the epidemic has yet to be determined. As of May 21, there were 92 confirmed cases of monkeypox; An additional 28 patients were suspected in 12 countries where it is not commonly seen. Australia, Canada, the USA, UK, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, and UAE are some of these countries. Although several of these boys sought treatment at primary care and sexual health clinics, where they had sexual contact with other men, none traveled to the local area.<sup>14-17</sup>

Other studies have shown similar results. 66 % of the 79 patients who were homosexual, bisexual, or otherwise cohabiting with other men, for a total of 86 cases, had no record of travel to a country with an active monkeypox epidemic May 7-25. Evidence of monkeypox virus DNA in the seminal fluid of four young Italian boys raises the possibility that they did not use condoms.

In the United States, 16 of 17 people whose sexual orientation was analyzed identified as gay, bisexual, or male, with sex only with other men. Increasing infections have been reported in the Americas, Africa, the Eastern Mediterranean, and the Western Pacific, while current outbreaks are concentrated in Europe.<sup>18-21</sup> Infections have also been discovered not too long ago in the Republic of the Congo, the Central African Republic, and Sudan; however, it is unknown whether these infections were caused by people moving across the border of the DRC or by the occurrence of a disease that was already present in those countries. Infections have also been discovered not too long ago in the Democratic Republic of the Congo (DRC). It is also uncertain if these illnesses were brought about by persons traveling over the border of the DRC or by the advent of a disease that was previously existing in those nations.<sup>22-24</sup> The advancement of phylogeographic and the georeferencing of human cases will be of aid in acquiring a better knowledge of the distribution of occurrences. These data have the potential to be used in the creation of ecological models of the transmission of monkeypox that are more accurate. In 2003, the United States saw a domestic epidemic of monkeypox that afflicted both people and prairie dogs that were kept as pets. The disease spreads from person to person via contact with infected prairie dogs.<sup>25,26</sup> An inquiry into the sequence of events led to the revelation that the most probable source of the illness was a shipment of wild rats from Ghana. This was determined as a result of the study.<sup>27,28</sup>

A fictional squirrel from the Democratic Republic of the Congo has been attacked by monkeys, as far as we know. As yet, we do not know how common the virus is or whether it is present in any animal. Mice infestation and making bushmeat is a common practice where rat and herbal meat are associated with human illness.<sup>29</sup> According to one theory, wounds, saliva/discharge, and direct contact with exudate or crustaceans may be the way to spread the disease. The feces of an infected person can infect you. Monkeypox can spread from person to person through contact, although it is less powerful than smallpox. Monkeypox has been caught among people who have never been vaccinated against smallpox.<sup>30</sup> Other times, but not usually, a continuous chain or

continuous transmission episode is attached to the patient's cluster. As a precaution, health workers and anyone else who may be exposed should be vaccinated. All healthcare workers exposed to the U.S. orthopoxvirus strain should be vaccinated with the orthopoxvirus vaccine.<sup>31</sup>

It is difficult to keep track of human monkeypox, where it is prevalent. Monkeypox can be difficult to detect due to a lack of samples, lack of infrastructure, and lack of diagnostic samples. It is essential to revisit the distinctive features of monkey Pox when new cases and past studies are discovered. In the case of monkeypox, for example, more precise descriptions can lead to more accurate diagnosis and treatment, as well as prevent the spread of the disease from one person to another by isolating infected people.<sup>32</sup> Healthcare professionals can help prevent and detect monkeypox by receiving frequent training. Expanding the lab-based disease monitoring network will help us better understand the spread of the disease. Since the introduction of the smallpox vaccine, humans have been protected from diseases such as the monkeypox (a vaccine using the virus).<sup>32</sup> Vaccination against smallpox was discontinued by the DRC in 1982. Orthopoxvirus infection is a possibility for those who were first vaccinated before 1982, as many of them have never been vaccinated and are at risk. The prevalence of human monkeypox in humans cannot be estimated as there is no vaccine for orthopoxvirus.<sup>33,34</sup>

The human monkeypox epidemic was studied in Ecuador from 1981 to 1986 when smallpox was declared extinct in the Democratic Republic of the Congo (DRC). As a result of past vaccinations, families were less likely to become infected. According to research, before vaccination (3-19 years ago), about 85% of all contacts were protected against monkeypox. Monkeypox is common at 0.63 per 10,000 people in the Bumba health area. The annual incidence of 5.53 cases per 10,000 in the Sankuru district of DRC has increased since last year. Only 24% and 4% of residents and monkeypox patients were previously vaccinated, which explains the current increase in infections. Orthopoxvirus infections can increase if these people are not vaccinated against the virus.<sup>35-37</sup> Six out of 29 people infected with smallpox in the United States were vaccinated against smallpox

as a child, indicating that the vaccine does not provide 100% protection. For these and other reasons, more research is needed on vaccination and how it affects the spread of the disease.<sup>38-40</sup>

A family returned to the UK in May 2021 after traveling to Nigeria, and three family members were ill with the monkeypox virus.<sup>41</sup> The sequential onset of symptoms in each family member may indicate human-to-human transmission. One incident occurred in July 2021, when a man traveled from Nigeria to Texas.<sup>42</sup> One incident occurred in November 2021, when a man traveled from Nigeria to Maryland.<sup>43</sup> A case of human monkeypox in men traveling from Canada to Massachusetts and a cohort of human monkeypox from the UK are under study until May 2022.<sup>44</sup> An increase in the number of monkeypox cases reported during the ongoing COVID-19 pandemic has further complicated the situation. In humans, SARS-CoV-2 infection can cause a wide range of symptoms, not just related to the respiratory system.<sup>45</sup> COVID-19 is associated with various skin manifestations, including erythematous maculopapular rash, vesicular rash, vascular lido reticularis, figure erythema, and flexural rash. Because of the apparent overlap of symptoms between COVID-19 and atypical monkeypox, clinicians should be alert for both during this outbreak.<sup>46</sup> It is also fairly unusual for many viruses, including SARS-CoV-2, to infect the same host. We thus cannot rule out the possibility of co-infection between SARS-CoV-2 and monkeypox virus. However, it is not known whether there is any change in the pattern, severity, treatment, or response to vaccination of any disease.<sup>47</sup> Therefore, additional studies are needed to determine whether COVID-19 is associated with monkeypox infection.

### Discovery of Monkeypox Virus

The genomes of the West African and Central African strains were compared, revealing a collection of potential genes that could be involved in viral variation across the entire clade. This discovery was made possible by a comparison of genomes. It has been speculated that the open text frames in question are the result of viral causes, changes in the viral life cycle, changes in the host range, immunosuppression, or all of these factors.<sup>48,49</sup> The Central African Monkeypox

virus suppresses T-cell receptor-mediated T-cell activation, causing human cells to release inflammatory cytokines that were previously produced by the infected person's cells.<sup>50</sup> This process occurs in human cells, which are formed by infected individuals. As a result of these discoveries, it appears that Monkey Pox may be able to create a modulator that inhibits host T-cell responses. Protecting the immune system against the Central African Monkeypox virus can be done in a variety of ways. The Central African strain of the monkeypox virus contains a gene known as the monkeypox virus inhibitor, a complementary enzyme.<sup>51</sup> This gene is an important immunomodulating factor that leads to larger viral levels. It has been speculated that the existence of a gene that inhibits complementary enzymes is responsible for the increased virus exhibited by viral strains originating in Central Africa. However, this gene does not exist in strains of the virus originating in West Africa. Also, monkeypox strains originating in Central Africa may be more likely to block the host response, especially host apoptosis. This feature distinguishes them from the monkeypox strains that originated in West Africa. These characteristics set Central African strains apart from their West African counterparts. Working together can lead to the discovery of individual differences in the levels of pathogenicity that have been found. In addition, transcriptional investigations have shown that when an infection occurs, the Central African monkeypox virus preferentially mutates a gene that is important for host immunity. It only occurs in infected people.<sup>52,53</sup> It is manifested throughout the disease. In order to establish the full range of effects that these different infections have on the body, it is essential that we make a concerted effort to work on different fronts at the same time. The monkeypox virus has only been found in non-human primates (NHPs) found in Africa's natural environment.<sup>54,55</sup> It seems that most of the monkeys that make their home in Africa have been infected with the virus at some point in their lives. Consequently, it is unfortunate that experimental research has not been carried out due to the limited availability of African monkeys. Instead, significant amounts of research have been done on *Sinomolgus* and Rhesus macaque, both indigenous to different regions of Asia where the Monkeypox

virus has never been detected.<sup>56</sup> African monkeys could not be tested because there were not enough primates. It is highly probable that this species of primate was chosen for a number of reasons, including the following: because it has been shown that these animals were susceptible to disease during previous outbreaks; Because these animals are readily available; Because these primates have been thoroughly investigated; And because they do well if the research is kept in the vivarium.<sup>57-59</sup> The virus responsible for monkeypox is shaped like a brick and has two strands of DNA inside. This result is positive because it implies that the virus is generally stable and less likely to mutate into a more lethal or easily spread form. Both of these outcomes would be undesirable. A single strand of RNA that the SARS-CoV-2 virus, which causes COVID-19, uses to make its genetic material. This virus is responsible for generating the disease.<sup>60</sup>

### Management

At this time, there is no particular therapy for monkeypox infection that has been shown effective in clinical trials. As is the case with the majority of viral diseases, the therapy consists of the management of supporting symptoms. However, there are preventative steps that can assist in preventing an epidemic from occurring.<sup>61</sup> The person who is infected should remain in isolation, wear a surgical mask, and keep lesions covered as much as is fairly possible till all crusts on the lesions have normally fallen off and a real skin surface has been established. During this time, the individual should also keep lesions covered as much as is reasonably possible. In severe situations, the medicines under investigation can be utilized. There is a lack of information about the effectiveness of the oral DNA polymerase inhibitor brincidofovir, the oral intracellular viral release inhibitor tecovirimat, and the intravenous vaccinia immune globulin against the monkeypox virus.<sup>62,63</sup> hence there is an urgent need to evaluate these medicines against monkeypox disease.

It has been shown that Orthopoxvirus species therapy can benefit from a variety of antiviral methods, including the application of a wide range of individual chemical compounds. An analysis of the chemical compounds that show the highest probability, in this case, can be found

**Table.** Treatments for Orthopoxvirus Infections that are intriguing

Antiviral Therapeutic	Mechanism of Action	Clinical Considerations	Ref.
Cidofovir	The presence of this chemical has an inhibiting effect on DNA polymerase	The medicine has been shown to cause neurotoxic effects when administered intravenously with hydrated and probenecid	76
CMX-001	Compound that was produced from cidofovir and underwent certain modifications; it acts as an inhibitor of DNA polymerase	Nephrotoxicity, as found with cidofovir, is absent; oral administration is possible	77
ST-246	Interferes with intracellular viral replication	Administered orally	67
Thymidine analogs (N- methano-carbathymidine)	DNA polymerization	Inhibition of viral DNA synthesis by orthopoxvirus thymidine kinase suppression	64

in Table. The antiviral activity of pseudofovir is quite effective against a wide range of different viruses discovered throughout the course of history.<sup>64</sup> This ability to inhibit the activity of DNA polymerase found in viruses is the main reason for the presence of this feature in the compound. Cidofovir has gone through a series of chemical transformations to give birth to a molecule now known as CMX-001. These adjustments were made to strengthen the defense against the virus responsible for hepatitis. CMX-001 did not show the same level of nephrotoxicity as pseudofovir when testing two drugs on the same battery. CMX-001 has antiviral properties that have been shown to be effective against various orthopoxviruses.<sup>65,66</sup> Several capabilities have been shown to be effective against this virus. Antiviral treatment with a drug known as ST-246 is effective against various orthopedic viruses, including the variola virus, which is one of them. This treatment is also effective against a number of other orthopoxvirus species. Also, it prevents the virus from escaping from the cell in which it is kept, which is a very important duty for it.<sup>67-70</sup> During clinical research, these drugs have been given in different combinations, especially with the vaccine immune globulin, which aims to reduce the more serious adverse effects associated with vaccination. Careful consideration should be given to the process of formulation of treatment strategies considering the application of the above pharmaceuticals in the geographical area where this condition is prevalent to ensure that all the

conditions described in this requirement are satisfied. To do this, it is necessary to ensure that all the conditions described in this requirement are satisfied. Because in order to meet these criteria, each of the requirements listed must be met.<sup>71-75</sup>

In these Epidemic individuals may have severe inguinal adenopathy in addition to sores in the vaginal, groin, perianal, or rectal areas. Because of this, it can be difficult to distinguish the illness from other types of STDs. Genital lesions have been documented in endemic populations, although the high fever previously characteristic of classic monkeypox was mild or nonexistent in these cases. Genital lesions have also been described. After a comprehensive risk assessment, healthcare professionals who have been exposed can receive individualized advice on self-monitoring, isolation, and prompt reporting of symptoms.<sup>78</sup> A thorough risk assessment can provide this information. When caring for a patient with an infectious condition, there is a significant risk of contracting the virus if the nurse chooses to remove the patient's bed sheets instead of checking the patient's vital signs or administering medication.<sup>79</sup>

Despite this, monkeypox has survived across Africa for decades without help from the rest of the world. Although clinical and public health institutions are already working at full capacity, dealing with the COVID-19 pandemic, the situation remains critical. People have repeatedly heard that they need to be careful and take precautions; They are sick and tired of hearing



this. Many people who spend their careers trying to improve the health and medical care of the general public are disappointed with the results of their work.<sup>80</sup> They may already be dealing with a significant amount of stress, and now they may have to contend with a potentially fatal new illness. Maintaining a high index of suspicion and following all relevant infection control standards are the two most important things health care workers can do to stop the spread of monkeypox and reduce the chance of it becoming a global pandemic. While infection control plans work to eradicate monkeypox, patients more susceptible to the illness should not feel ashamed.<sup>79,81</sup>

## CONCLUSION

There are several new infectious diseases that we know almost nothing about. Based on what we learned during the COVID-19 pandemic, scientists can be certain that the frequency with which new viruses cause human illness will increase. The rising number of monkeypox infections in the United States and several European countries provides evidence that zoonotic reservoirs may play a role in the spread of the virus. There is a possibility that the virus could spread to areas where monkeys do not currently exist or that individuals may gain weight and place themselves in a position where they are more likely to come into contact with wildlife. Another possibility is that the virus could cause people to become infected with monkeypox as they gain weight. The monkeypox virus could potentially be transmitted through any of these situations. Both of these situations increase the level of tension in the case. The primary causes of each of these disasters can be traced to the instability within the population and the movement of victims. The significant increase in the number of human diseases calls for further studies as well as investigations and inspections to better understand the various aspects contributing to the disease's transmission and development. Many problems related to human ponds, animal ponds, and viral infections still need to be solved.

## ACKNOWLEDGMENTS

None.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

NN and TBE conceptualized and designed the work. NN performed the literature survey and wrote the manuscript. KD reviewed and edited the manuscript. All authors read and approved the final manuscript for publication.

## FUNDING

None.

## DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

## ETHICS STATEMENT

Not applicable.

## REFERENCES

1. Adegboye OA, Castellanos ME, Alele FO, et al. Travel-related monkeypox outbreaks in the era of COVID-19 pandemic: are we prepared? *Viruses*. 2022;14(6):1283. doi: 10.3390/v14061283
2. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ*. 1972;46:593.
3. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Eng J Med*. 2002;346(17):1300-1308. doi: 10.1056/NEJMra020025
4. Shafaati M, Zandi M. Monkeypox virus neurological manifestations in comparison to other orthopoxviruses. *Travel Med Infect Dis*. 2022;49:102414. doi: 10.1016/j.tmaid.2022.102414
5. Lai CC, Hsu CK, Yen MY, Lee PI, Ko WC, Hsueh PR. Monkeypox: An emerging global threat during the COVID-19 pandemic. *J Microbiol Immunol Infect*. 2022;55(5):787-794. doi: 10.1016/j.jmii.2022.07.004
6. Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. Human monkeypox: secondary attack rates. *Bull World Health Organ*. 1988;66(4):465-470:465. PMID: PMC2491159
7. Meyer H, Perrichot M, Stemmler M, et al. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. *J Clin Microbiol*. 2002;40(8):2919-2921. doi: 10.1128/JCM.40.8.2919-2921.2002
8. Islam F, Dhawan M, Emran TB. Unusual spread of the monkeypox virus: An emerging threat to the public health and the possible containment. *Ann Med Surg*. 2022;82: 104580. doi: 10.1016/j.amsu.2022.104580
9. Mohapatra RK, Tuli HS, Sarangi AK, et al. Unexpected

- sudden rise of human monkeypox cases in multiple non-endemic countries amid COVID-19 pandemic and salient counteracting strategies: Another potential global threat? *Int J Surg.* 2022;103:106705. doi: 10.1016/j.ijsu.2022.106705
10. Breman JG, Steniowski M V, Zanutto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. *Bull World Health Organ.* 1980;58(2):165. PMID: PMC2395797
  11. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis.* 1987;156(2):293-298. doi: 10.1093/infdis/156.2.293
  12. Fine PEM, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. *Int J Epidemiol.* 1988;17(3):643-650. doi: 10.1093/ije/17.3.643
  13. Reynolds MG, Damon IK. Outbreaks of human monkeypox after cessation of smallpox vaccination. *Trends Microbiol.* 2012;20(2):80-87. doi: 10.1016/j.tim.2011.12.001
  14. Ferraro F, Caraglia A, Rapiti A, et al. multiple introductions of MPX in Italy from different geographic areas. *Euro Surveill.* 2022;27(33):2200456. doi: 10.2807/1560-7917.ES.2022.27.23.2200456
  15. Monkeypox - United Kingdom of Great Britain and Northern Ireland. 2022. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON383>
  16. Vallee A, Farfour E, Zucman D. Monkeypox virus: A novel sexually transmitted disease? A case report from France. *Travel Med Infect Dis.* 2022;49:102394. doi: 10.1016/j.tmaid.2022.102394
  17. Dhawan M, Emran TB, Islam F. The resurgence of monkeypox cases: Reasons, threat assessment, and possible preventive measures. *Travel Med Infect Dis.* 2022;49:102367. doi: 10.1016/j.tmaid.2022.102367
  18. Isidro J, Borges V, Pinto M, et al. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. *Nat Med.* 2022;28(10):2220-2221. doi: 10.1038/s41591-022-02036-2
  19. Minhaj FS, Ogale YP, Whitehill F, et al. Monkeypox outbreak-nine states, May 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(23):764-769. doi: 10.15585/mmwr.mm7123e1
  20. Antinori A, Mazzotta V, Vita S, et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. *Euro Surveill.* 2022;27(22):2200421. doi: 10.2807/1560-7917.ES.2022.27.22.2200421
  21. Vivancos R, Anderson C, Blomquist P, et al. Community transmission of monkeypox in the United Kingdom, April to May 2022. *Euro Surveill.* 2022;27(22):2200422. doi: 10.2807/1560-7917.ES.2022.27.22.2200422
  22. Lash RR, Carroll DS, Hughes CM, et al. Effects of georeferencing effort on mapping monkeypox case distributions and transmission risk. *Int J Health Geogr.* 2012;11:1-12. doi: 10.1186/1476-072X-11-23
  23. Ellis CK, Carroll DS, Lash RR, et al. Ecology and geography of human monkeypox case occurrences across Africa. *J Wildl Dis.* 2012;48(2):335-347. doi: 10.7589/0090-3558-48.2.335
  24. Ellis CK. Ecology and geography of human monkeypox case occurrences across Africa. 2008.
  25. Learned LA, Reynolds MG, Wasswa DW, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. *Am J Trop Med Hyg.* 2005;73(2):428-434. doi: 10.4269/ajtmh.2005.73.428
  26. Formenty P, Muntasir MO, Damon I, et al. Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. *Emerg Infect Dis.* 2010;16(10):1539-1545. doi: 10.3201/eid1610.100713
  27. Berthet N, Nakoune E, Whist E, et al. Maculopapular lesions in the Central African Republic. *Lancet.* 2011;378(9799):1354. doi: 10.1016/S0140-6736(11)61142-2
  28. Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the Western Hemisphere. *N Engl J Med.* 2004;350(4):342-350. doi: 10.1056/NEJMoa032299
  29. Khodakevich L, Jezek Z, Kinzanzka K. Isolation of monkeypox virus from wild squirrel infected in nature. Isolation of monkeypox virus from wild squirrel infected in nature. *Lancet.* 1986;1(8472):98-99. doi: 10.1016/S0140-6736(86)90748-8
  30. Reynolds MG, Carroll DS, Karem KL. Factors affecting the likelihood of monkeypox's emergence and spread in the post-smallpox era. *Curr Opin Virol.* 2012;2(3):335-343. doi: 10.1016/j.coviro.2012.02.004
  31. Hutson CL, Olson VA, Carroll DS, et al. A prairie dog animal model of systemic orthopoxvirus disease using West African and Congo Basin strains of monkeypox virus. *J Gen Virol.* 2009;90(Pt 2):323-333. doi: 10.1099/vir.0.005108-0
  32. Hutson CL, Carroll DS, Self J, et al. Dosage comparison of Congo Basin and West African strains of monkeypox virus using a prairie dog animal model of systemic orthopoxvirus disease. *Virology.* 2010;402(1):72-82. doi: 10.1016/j.virol.2010.03.012
  33. Fleischauer AT, Kile JC, Davidson M, et al. Evaluation of human-to-human transmission of monkeypox from infected patients to health care workers. *Clin Infect Dis.* 2005;40(5):689-694. doi: 10.1086/427805
  34. Rotz LD, Dotson DA, Damon IK, Becher JA. Vaccinia (smallpox) vaccine; recommendations of the Advisory Committee Immunization Practices (ACIP), 2001.
  35. Leggiadro RJ. Major Increase in Human Monkeypox Incidence 30 Years After Smallpox Vaccination Campaigns Cease in the Democratic Republic of Congo: AW Rimoin et al. PNAS: Published online before print August 30, 2010. *Pediatr Infect Dis J.* 2011;30(1):2. doi: 10.1097/INF.0b013e3181fe2eb7
  36. Damon IK, Roth CE, Chowdhary V. Discovery of monkeypox in Sudan. *N Engl J Med.* 2006;355(9):962-963. doi: 10.1056/NEJMc060792
  37. Estep RD, Messaoudi I, O'Connor MA, et al. Deletion of the monkeypox virus inhibitor of complement enzymes locus impacts the adaptive immune response to monkeypox virus in a nonhuman primate model of infection. *J Virol.* 2011;85(18):9527-9542. doi: 10.1128/JVI.00199-11
  38. Karem KL, Reynolds M, Hughes C, et al. Monkeypox-



- induced immunity and failure of childhood smallpox vaccination to provide complete protection. *Clin Vaccine Immunol.* 2007;14(10):1318-1327. doi: 10.1128/CVI.00148-07
39. Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis.* 2005;41(12):1742-1751. doi: 10.1086/498115
40. Lewis MW, Graham MB, Hammarlund E, Hanifin J, Slifka MK. Monkeypox without exanthem. *N Engl J Med.* 2007;356(20):2112-2114. doi: 10.1056/NEJMc062788
41. Hobson G, Adamson J, Adler H, et al. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021. *Euro Surveill.* 2021;26(32):2100745. doi: 10.2807/1560-7917.ES.2021.26.32.2100745
42. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a traveler returning from Nigeria-Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71(14):509-516. doi: 10.15585/mmwr.mm7114a1
43. Costello V, Sowash M, Gaur A, et al. Imported Monkeypox from International Traveler, Maryland, USA, 2021 (Response). *Emerg Infect Dis.* 2022;28(8):1739. doi: 10.3201/eid2808.220830
44. Mahase E. Monkeypox: What do we know about the outbreaks in Europe and North America? *BMJ.* 2022;277:01274. doi: 10.1136/bmj.o1274
45. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. *Int J Antimicrob Agents.* 2020;56(2):106024. doi: 10.1016/j.ijantimicag.2020.106024
46. Mohammed GF, Al-Dhubaibi MS, Atef L. Cutaneous Manifestations of Coronavirus Disease 2019: Skin Narratives and Dialogues. *J Clin Aesthet Dermatol.* 2022;15(5):E77-E81. PMID: PMC9122281
47. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect.* 2020;53(4):505-512. doi: 10.1016/j.jmii.2020.05.013
48. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. *J Gen Virol.* 2005;86(Pt 10):2661-2672. doi: 10.1099/vir.0.81215-0
49. Saijo M, Ami Y, Suzaki Y, et al. Virulence and pathophysiology of the Congo Basin and West African strains of monkeypox virus in non-human primates. *J Gen Virol.* 2009;90(Pt 9):2266-2271. doi: 10.1099/vir.0.010207-0
50. Reynolds MG, Yorita KL, Kuehnert MJ, et al. Clinical manifestations of human monkeypox influenced by route of infection. *J Infect Dis.* 2006;194(6):773-780. doi: 10.1086/505880
51. Hammarlund E, Dasgupta A, Pinilla C, Norori P, Fruh K, Slifka MK. Monkeypox virus evades antiviral CD4+ and CD8+ T cell responses by suppressing cognate T cell activation. *Proc Natl Acad Sci U S A.* 2008;105(38):14567-14572. doi: 10.1073/pnas.0800589105
52. Hudson PN, Self J, Weiss S, et al. Elucidating the role of the complement control protein in monkeypox pathogenicity. *PLoS One.* 2012;7(4):e35086. doi: 10.1371/journal.pone.0035086
53. Breman JG, Nakano JH, Coffi E, Godfrey H, Gautun JC. Human poxvirus disease after smallpox eradication. *Am J Trop Med Hyg.* 1977;26(2):273-281. doi: 10.4269/ajtmh.1977.26.273
54. Carroll DS, Emerson GL, Li Y, et al. Chasing Jenner's vaccine: revisiting cowpox virus classification. *PLoS One.* 2011;6(8):e23086. doi: 10.1371/journal.pone.0023086
55. Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology.* 2005;340(1):46-63. doi: 10.1016/j.virol.2005.05.030
56. Kindrachuk J, Arsenault R, Kusalik A, et al. Systems kinomics demonstrates Congo Basin monkeypox virus infection selectively modulates host cell signaling responses as compared to West African monkeypox virus. *Mol Cell Proteomics.* 2012;11(6):M111.015701. doi: 10.1074/mcp.M111.015701
57. Rubins KH, Hensley LE, Reiman DA, Brown PO. Stunned silence: gene expression programs in human cells infected with monkeypox or vaccinia virus. *PLoS One.* 2011;6(1):e15615. doi: 10.1371/journal.pone.0015615
58. Wenner HA, Kamitsuka P, Macasaet F, Kidd P. Pathogenesis of monkey pox. *Antimicrob Agents Chemother.* 1967;7:40-44.
59. Shchelkunov SN, Totmenin AV, Babkin IV, et al. Human monkeypox and smallpox viruses: genomic comparison. *FEBS Lett.* 2001;509(1):66-70. doi: 10.1016/S0014-5793(01)03144-1
60. What is monkeypox and why is it spreading? BBC Future. <https://www.bbc.com/future/article/20220801-what-is-monkeypox-and-why-is-it-spreading>
61. McCollum AM, Damon IK. Human monkeypox. *Clin Infect Dis.* 2014;58(2):260-267. doi: 10.1093/cid/cit703
62. Petersen BW, Kabamba J, McCollum AM, et al. Vaccinating against monkeypox in the Democratic Republic of the Congo. *Antiviral Res.* 2019;162:171-177. doi: 10.1016/j.antiviral.2018.11.004
63. Kozlov M. Monkeypox goes global: why scientists are on alert. *Nature.* 2022;606(7912):15-16. doi: 10.1038/d41586-022-01421-8
64. Parker S, Handley L, Buller RM. Therapeutic and prophylactic drugs to treat orthopoxvirus infections. *Future Virol.* 2008;3(6):595-612. doi: 10.2217/17460794.3.6.595
65. Atrasheuskaya AV, Bukin EK, Fredeking TM, Ignatyev GM. Protective effect of exogenous recombinant mouse interferon-gamma and tumour necrosis factor-alpha on ectromelia virus infection in susceptible BALB/c mice. *Clin Exp Immunol.* 2004;136(2):207-14. doi: 10.1111/j.1365-2249.2004.02460.x
66. Nuara AA, Buller RML, Bai H. Identification of residues in the ectromelia virus gamma interferon-binding protein involved in expanded species specificity. *J Gen Virol.* 2007;88(Pt 1):51-60. doi: 10.1099/vir.0.82324-0
67. Lederman ER, Davidson W, Groff HL, et al. Progressive vaccinia: case description and laboratory-guided therapy with vaccinia immune globulin, ST-246, and CMX001. *J Infect Dis.* 2012;206(9):1372-1385. doi: 10.1093/infdis/jis510
68. Artenstein AW, Johnson C, Marbury TC, et al. A novel,

- cell culture-derived smallpox vaccine in vaccinia-naive adults. *Vaccine.* 2005;23(25):3301-3309. doi: 10.1016/j.vaccine.2005.01.079
69. Reynolds MG, Emerson GL, Pukuta E, et al. Detection of human monkeypox in the Republic of the Congo following intensive community education. *Am J Trop Med Hyg.* 2013;88(5):982. doi: 10.4269/ajtmh.12-0758
70. Nakazawa Y, Emerson GL, Carroll DS, et al. Phylogenetic and ecologic perspectives of a monkeypox outbreak, southern Sudan, 2005. *Emerg Infect Dis.* 2013;19(2):237-245. doi: 10.3201/eid1902.121220
71. Vora S, Damon I, Fulginiti V, et al. Severe eczema vaccinatum in a household contact of a smallpox vaccinee. *Clin Infect Dis.* 2008;46(10):1555-1561. doi: 10.1086/587668
72. Monath TP, Caldwell JR, Mundt W, et al. ACAM2000 clonal Vero cell culture vaccinia virus (New York City Board of Health strain)-a second-generation smallpox vaccine for biological defense. *Int J Infect Dis.* 2004;8(Suppl 2):S31-44. doi: 10.1016/j.ijid.2004.09.002
73. Weltzin R, Liu J, Pugachev KV, et al. Clonal vaccinia virus grown in cell culture as a new smallpox vaccine. *Nat Med.* 2003;9(9):1125-1130. doi: 10.1038/nm916
74. Marriott KA, Parkinson CV, Morefield SI, Davenport R, Nichols R, Monath TP. Clonal vaccinia virus grown in cell culture fully protects monkeys from lethal monkeypox challenge. *Vaccine.* 2008;26(4):581-588. doi: 10.1016/j.vaccine.2007.10.063
75. Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions; guidance for clinicians. 2003. Prevention C for DC and. Vaccinia (smallpox) vaccine, recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *Mortal Morb Wkly Rep.* 2001;50:1-25.
76. Petersen BW, Damon IK, Pertowski CA, et al. Clinical guidance for smallpox vaccine use in a postevent vaccination program. *MMWR Morb Mortal Wkly Rep.* 2015;64:1-26.
77. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis.* 2020;71(8):e210-4. doi: 10.1093/cid/ciaa143
78. Duque MP, Ribeiro S, Martins JV, et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. *Euro Surveill.* 2022;27(22):2200424. doi: 10.2807/1560-7917.ES.2022.27.22.2200424
79. O'Shea J. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection-United States, August 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(32):1023-1028. doi: 10.15585/mmwr.mm7132e4
80. Palmore TN, Henderson DK. Adding New Fuel to the Fire: Monkeypox in the Time of COVID-19- Implications for Health Care Personnel. *Ann Intern Med.* 2022;175(8):1183-1184. doi: 10.7326/M22-1763